

REMARKS

Applicants initially would like to thank Examiner Marschel for his time spent in the June 29, 1993 telephone interview with Dr. Aaronson, Dr. Kraus and applicants' undersigned attorney. The interview was very helpful to fully discuss the claim amendments, new claims and outstanding utility rejection.

Claims 44-47 and 60 are currently pending. Claim 44 has been amended to clarify the claim and emphasize that the cancer can be evaluated by determining whether it is caused by an amplification or increased expression. Such amendment is clearly enabled throughout the specification which teaches cancers can be evaluated and classified as those caused or not caused by an amplification or increased expression or a MAC117 gene.

New Claim 61 has been added to include a method of classifying cancers based on the presence of amplification or increased expression of MAC117. The specification clearly supports that MAC117 amplification can be detected and used to classify those cancers having amplification.

New Claim 62 claims a method of determining the progression of a tumor to a more malignant tumor. Support for this concept is provided on page 23, lines 14-27. As agreed in the interview, more malignant means a cancer which is more

harmful such that a patient having such a cancer has a decreased chance of survival. Of the new claims, only Claim 62 corresponds to the count set forth in the applicants' November 6, 1991 Request for Interference.

In the February 9, 1993 Office Action, claims 44-47 and 60 stand rejected as allegedly lacking the utility diagnosing or evaluating the presence of cancer in a human. The Office Action then goes on to evaluate each reference cited by the applicants' December 2, 1991 amendment.

Applicants initially wish to point out that claim 44 is directed to diagnosing or evaluating human cancer in a patient. Applicants very clearly have shown that a cancer can be evaluated by determining if the cancer results from amplification or increased expression of the MAC117 gene. This evaluation alone, independent of diagnosis of the cancer, is of sufficient utility to satisfy 35 U.S.C. § 101. Being able to classify the type of cancer is useful to an oncologist studying cancers. Applicants wish to emphasize that such classification is not an invitation to do further research but rather a presently available means to catalogue and distinguish different types and forms of cancer.

The evaluation of a cancer as caused or not caused by the amplification or increased expression of the MAC117 gene also allows the prognosis of a patient's chances of survival. Applicants note that they are not claiming prognosis per se in Claim 61, but

the step of evaluating the cancer prior to making the association of the amplification with patient survival. However, since the evaluation of the cancer as caused by amplification or increased expression allows the prognosis of a patient, an additional utility is provided for evaluating a cancer. The utility for evaluating a more malignant phenotype is apparent, as described in new Claim 62. The utility for prognosis was previously recognized by the Examiner on page 4, lines 16 – 19 of the June 2, 1992 Office Action. Thus, utility for new Claim 62 is not an issue. However, to emphasize the utility for being able to determine a more malignant phenotype, applicants enclose herewith Slamon *et al.* (1987), Slamon *et al.* (1989), Tandon *et al.* (1989), Paterson *et al.* (1991), Gusterson *et al.* (1988), Walker *et al.* (1989), Borg *et al.* (1990), Wistanley *et al.* (1990), O'Reilly *et al.* (1990), Gullick *et al.* (1990) and Lovekin *et al.* (1990), as Exhibits 1 – 11.

Finally, applicants maintain that utility for diagnosis of a cancer is also provided. In addition to the papers cited in applicants December 2, 1992 amendment, namely Varmus, Bargmann *et al.*, De Fiore *et al.*, Hudziak *et al.*, Muller *et al.*, Paik *et al.*, Lacroix *et al.*, Inglehart *et al.*, Yokota *et al.*, Zhou *et al.*, Varley *et al.*, Press *et al.*, applicants further provide references to textbooks of Internal Medicine, Cancer, and Genetics are provided (Exhibit 12 – 16). These citations as requested by the Examiner demonstrate that gene amplification represents a widely accepted mechanism for oncogene activation. Furthermore, the paper by Gusterson *et al.* (Exhibit 5) contains more examples of non-cancerous cells lacking amplification/overexpression of this proto-

oncogene. This study includes 149 cases of benign lesions unequivocally demonstrating that amplification/overexpression occurs "only in cells that are cytologically malignant" (summary, line 11).

Moreover, since (1) proto-oncogene amplification is only found when a gene is an active oncogene and (2) additional data is presented showing proto-oncogene amplification/overexpression does not occur in non-malignant cells, the correlations of amplification and cancer for *erb-B2* (MAC117) set forth in the cited references demonstrate the claimed methods are useful.

Applicants also respectfully point out that the method utilized to detect amplification does not result in false positives due to internal standardization with a reference probe (Kraus *et al.*, 1987 (Exhibit 17)); Slamon *et al.* 1989 (Exhibit 2)).

In addition, the utility of the claimed invention is provided by the successful sale of the reagents to diagnose the presence of the amplification or overexpression. As one example, Molecular Oncology Inc. clinical laboratory performed \$7,000 in clinical *erbB-2* testing during January and February of 1993. The catalogues for Oncor and Oncogene Sciences include reagents/kits for use in measuring *erbB-2* gene amplification/overexpression in breast and ovarian cancer.

Finally, applicants wish to address certain of the comments set forth in the February 9, 1993 Office Action, pertaining to the references provided in applicants' December 2, 1992 amendment.

The Examiner notes that Varmus fails to observe transforming activity in 80–90% of tumors. In addition, the Examiner states that the Yokota *et al.* observation of amplification of c-erb-2 in 5 of 63 adenocarcinomas is "hardly persuasive of significant correlation." Finally, the Examiner notes that Varley *et al.* showed neu amplification in "only 19% of their carcinoma samples." Applicants assert that all that needs to be shown is that the amplification can be used to diagnose cancer. Very clearly, the case law does not require the method to be tremendous or better than prior methods. The law merely requires that the method be useful (see, e.g., Carpet Seaming Tape Licensing Corp. v. Best Seam, Inc., 694 F.2d 570, 216 U.S.P.Q. 873 (9th Cir. 1982) ("the fact that an invention has only limited utility and is only operable in certain applications has not been regarded as grounds for finding a patent invalid for lack of utility"); Studiengesellschaft Kohle v. Eastman Kodak Co., 616 F.2d 1315, 1339, 206 U.S.P.Q. 577 (5th Cir. 1980) ("To require the product to be the victor in the competition of the marketplace is to impose upon patentees a burden far beyond that expressed in the statute."); Cusano v. Kotler, 159 F.2d 159, 162, 72 U.S.P.Q. 62 (3d Cir. 1946); Boyce v. Stewart-Warner Speedometer Corp., 200 F.118, 126 (2d Cir. 1914); Laitram Corp. v. Depoe Bay Fish Co., 549 F. Supp. 29 (D. Ore. 1982); Imperial Chem. Indus., PLC v. Henkel Corp., 545 F. Supp. 635 (D.

Del. 1982) ("commercial success is not the standard of usefulness under the Patent Act");
Cf. Nickola V. Peterson, 580 F.2d 898, 198 U.S.P.Q. 385 (6th Cir. 1978) (there is no
requirement of patent law that an invention achieve a new result or function)).

Thus, even though amplification was found in only 5 of 63
adenocarcinomas by Yokota *et al.* and 19% of carcinomas by Varley *et al.* these
references provide very clear evidence that amplification can be used for diagnosis. Even
if these results indicated that it may not be economically prudent to base a diagnostic test
on these cancers, the case law is very clear that such is not what is required for utility.
However, as noted above, the reagents to carry out the claimed invention are being
purchased and used by industry. Moreover, these references clearly show that the
claimed method in fact can be performed and utility, therefore, is clearly demonstrated,
especially in view of the additional reference discussed above.

Pursuant to the above amendments and remarks, reconsideration and
allowance of the pending application is believed to be warranted. The Examiner is
invited and encouraged to directly contact the undersigned if such contact may enhance
the efficient prosecution of this application to issue.

A check in the amount of \$840.00 is attached as required for the extension of time. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.



Respectfully submitted,

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CERTIFICATE OF MAILING

I hereby certify that the foregoing AMENDMENT is being deposited with the United States Postal Service as first class mail in an envelope addressed to:

Commissioner of Patents
and Trademarks
Washington, D.C. 20231

on this 9th day of August 1993.

David G. Perryman 8-9-93
David G. Perryman DATE